Meat Consumption and Risk of Colorectal Cancer

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Context Consumption of red and processed meat has been associated with colorectal cancer in many but not all epidemiological studies; few studies have examined risk in relation to long-term meat intake or the association of meat with rectal cancer.

Objective To examine the relationship between recent and long-term meat consumption and the risk of incident colon and rectal cancer.

Design, Setting, and Participants A cohort of 148 610 adults aged 50 to 74 years (median, 63 years), residing in 21 states with population-based cancer registries, who provided information on meat consumption in 1982 and again in 1992/1993 when enrolled in the Cancer Prevention Study II (CPS II) Nutrition Cohort. Follow-up from time of enrollment in 1992/1993 through August 31, 2001, identified 1667 incident colorectal cancers. Participants contributed person-years at risk until death or a diagnosis of colon or rectal cancer.

Main Outcome Measure Incidence rate ratio (RR) of colon and rectal cancer.

Results High intake of red and processed meat reported in 1992/1993 was associated with higher risk of colon cancer after adjusting for age and energy intake but not after further adjustment for body mass index, cigarette smoking, and other covariates. When long-term consumption was considered, persons in the highest tertile of consumption in both 1982 and 1992/1993 had higher risk of distal colon cancer associated with processed meat (RR, 1.50; 95% confidence interval [CI], 1.04-2.17), and ratio of red meat to poultry and fish (RR, 1.53; 95% CI, 1.08-2.18) relative to those persons in the lowest tertile at both time points. Long-term consumption of poultry and fish was inversely associated with risk of both proximal and distal colon cancer. High consumption of red meat reported in 1992/1993 was associated with higher risk of rectal cancer (RR, 1.71; 95% CI, 1.15-2.52; $P=.007$ for trend), as was high consumption reported in both 1982 and 1992/1993 (RR, 1.43; 95% CI, 1.00-2.05).

Conclusions Our results demonstrate the potential value of examining long-term meat consumption in assessing cancer risk and strengthen the evidence that prolonged high consumption of red and processed meat may increase the risk of cancer in the distal portion of the large intestine.

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MEAT CONSUMPTION HAS been associated with colorectal neoplasia in the epidemiological literature, but the strength of the association and types of meat involved have not been consistent. Few studies have evaluated long-term meat consumption or the relationship between meat consumption and the risk of rectal cancer. Studies of red meat consumption and colorectal adenoma have reported odds ratios in the range of 1.2 to 1.3.[1-3] Case-control studies[4-25] of colorectal cancer conducted in the United States and Europe have generally reported increased risk associated with red or processed meat intake in analyses of men,[4-9,13,14] and men and women combined,[10-12,15-25] but not in analyses that included only women.[5-9,13] Case-control studies[26-32] of colorectal cancer among Asians in the United States or Asia have more consistently reported a positive association with red, processed, or total meats.

Five[33-37] of 10[33-42] US prospective studies of colorectal cancer reported positive associations with red or processed meat intake, although some associations[35-37] did not reach statistical significance. European prospective studies[43-49] have generally reported no association with fresh or total meat but positive associations with cured or processed meat,[43,45,46] sausages,[47] or smoked/salted fish.[45] High consumption of poultry or fish has been inconsistently associated with higher[36,37,46] or lower[34,40,41,47,49] risk of colorectal cancer; some studies have found no association.[33,39,42,43,45,48] Only 2 prospective studies[38,49] have reported on rectal cancer in relation to meat consumption. The results were conflicting but were limited by the small number of cases.

See also pp 183 and 233.

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A meta-analysis[50] of case-control and prospective studies estimated the mean relative risk comparing the highest to lowest categories of meat consumption to be 1.35 (95% confidence interval [CI], 1.21-1.51) for red meat and 1.31 (95% CI, 1.13-1.51) for processed meat and colorectal cancer. A review of prospective studies[51] concluded that a daily increment of 100 g of red or total meat consumption was associated with a 12% to 17% higher risk of colorectal cancer, and that an increment of 25 g of processed meat was associated with a 49% higher risk. Not all risk estimates included in these review articles were adjusted for potential confounders beyond age and energy intake, so residual confounding may influence the summary risk estimates.

Clarifying the role of meat consumption in colorectal carcinogenesis is important. Meat is an integral component of diet in the United States and many other countries in which colorectal cancer is common. Per capita annual consumption of beef has increased in the United States since 1993, reversing a previous decrease since 1976. Poultry consumption has surpassed beef consumption since the late 1980s.[52,53]

An earlier analysis of the Cancer Prevention Study II (CPS II) Mortality Cohort, based on deaths from colorectal cancer from 1982 to August 1988, found no association between colorectal cancer mortality and high consumption of red meat, but suggested lower risk associated with higher intake of chicken and fish in women.[41] We examined the relationship between meat consumption and incident colon and rectal cancers among 148 610 men and women enrolled in the CPS II Nutrition Cohort in 1992/1993.

METHODS

Study Population

The CPS II Nutrition Cohort has been described in detail elsewhere.[54] Briefly, the CPS II Nutrition Cohort comprised 86 404 men and 97 786 women who completed a mailed questionnaire in 1992/1993 and were followed up for cancer incidence and mortality. This cohort is a subset of the CPS II Mortality Cohort in which 1.2 million US adults from all 50 states, Puerto Rico, and the District of Columbia have been followed up for cancer mortality since 1982.[54] In the CPS II Mortality Cohort, participants completed a self-administered questionnaire in 1982 with information on diet, exercise, medical history, and other lifestyle habits. Race was determined on this 1982 questionnaire by multiple choice (white, black, Hispanic, Oriental, and other). Enrollment in the CPS II Nutrition Cohort was limited to men and women aged 50 to 74 years, residing in 21 states with population-based cancer registries that demonstrated at least 90% ascertainment of incident cancers by 1990. The median age at the CPS II Nutrition Cohort enrollment was 63 years.

The 1992/1993 CPS II Nutrition Cohort questionnaire obtained information on diet, physical activity, medical history, and other lifestyle habits. This cohort was recontacted at 2-year intervals between 1997 and 2003 with self-administered questionnaires to update information on newly diagnosed cancers, medical history, and lifestyle factors. Reported cancer diagnoses through 2001 have been verified by clinical information obtained from medical records or linkage with state cancer registries. An earlier study linking CPS II Nutrition Cohort participants to state cancer registries demonstrated that self-report of any cancer could identify incident cancers with a sensitivity of 93%.[55] Mortality follow-up of the entire CPS II Nutrition Cohort[54] is ongoing through automated linkage with the National Death Index. Cohort participants on average report higher educational attainment and more behaviors suggesting health consciousness than the general US population.[54] Participants were informed of data linkage activities on each mailed questionnaire and provided written consent by returning the completed questionnaire. All aspects of the CPS II study protocol were approved by the Emory University Institutional Review Board.

This analysis was based on 1667 incident cases of colon or rectal cancer diagnosed from the time of enrollment in 1992/1993 through August 31, 2001. Participants contributed person-years at risk until death or a diagnosis of colon or rectal cancer. Excluded from the analysis were persons who were not known to be deceased but failed to respond to the 1997, 1999, and 2001 questionnaires (3.7%); reported a colon or rectal cancer not verified by pathology report or death certificate (0.3%); reported at baseline a personal history of colon or rectal cancer (1.5%); reported uninterpretable or missing data on meat consumption in 1982 (4.7%); completed less than 85% of the food section of the 1992/1993 questionnaire; or reported implausibly high or low energy intake (9.1%). After exclusions, the analytic cohort included 69 664 men and 78 946 women, representing 81% of the CPS II Nutrition Cohort.

Incident Colon and Rectal Cancer

A total of 1197 incident cancers of the colon (*International Classification of Diseases* codes: C18.0, C18.2-C18.9)[56,57] and 470 cancers of the rectosigmoid junction (C19.0)[56,57] or rectum (C20.9)[56,57] were identified. Of these, 665 colon and 291 rectal cancers were diagnosed in men, and 532 colon and 179 rectal cancers in women. A total of 1335 (80%) of 1667 colorectal cancers were self-reported on the 1997, 1999, or 2001 questionnaires and subsequently verified by medical record abstraction or linkage with state cancer registries; another 43 (3%) were identified while verifying a different reported cancer; and 289 (17%) were identified as interval deaths, defined as persons who died with colon or rectal cancer recorded on death certificate but not reported on the questionnaire. Linkage with state cancer registries confirmed the diagnosis of colon or rectal cancer in 74% of interval deaths. Subsite-specific analyses were conducted on 667 proximal (cecum to splenic flexure) and 408 distal (descending to sigmoid colon) colon cancers, excluding those with overlapping or unspecified site codes. We also present the results

from analyses of 470 cancers of the rectosigmoid and rectum combined but not from separate analyses of the rectosigmoid junction (214 cases) or rectum (246 cases). The remaining 10 cases were unspecified (not able to distinguish as rectum or rectosigmoid junction).

Meat Consumption

Dietary assessment in 1992/1993 was based on a 68-item modified Block[58] food-frequency questionnaire (FFQ); nutrient values were estimated using the Dietary Analysis System version 3.8a.[59] Participants were asked to report their usual eating habits during the past year, including average frequency and serving size (small, medium, or large) of each food and beverage listed. Consumption of each meat item in grams per week was estimated by taking the product of average frequency per week, number of grams in a medium serving, and serving size (0.5 for small, 1.0 for medium, and 1.5 for large). Intake of red meat, poultry and fish, and processed meat (g/wk) was computed by summing across meat items that contributed to each meat group and categorizing by quintile. The lowest quintile of intake served as the referent group for analyses.

We considered red meat to include the following individual or grouped items on the questionnaire: bacon; sausage; hamburgers, cheeseburgers, meatloaf, or casserole with ground beef; beef (steaks, roasts, etc, including sandwiches); beef stew, or pot pie with carrots or other vegetables; liver, including chicken livers; pork, including chops, roast; hot dogs; and ham, bologna, salami, or lunchmeat. Food items classified as poultry and fish included chicken or turkey (roasted, stewed, broiled, ground, including sandwiches); fried chicken; fried fish or fish sandwich; tuna, tuna salad, tuna casserole; and other fish (broiled or baked). We considered processed meat to include bacon; sausage; hot dogs; and ham, bologna, salami, or lunchmeat. We computed the ratio of red meat-to-poultry and fish by dividing red meat intake by intake of poultry and fish (g/wk); individuals were assigned to the lowest or highest quintile when either value was 0. An additional question, "How often did you eat beef, pork, or lamb as a main dish, eg, steak, roast ham, etc (4-6 ounces)?" was included for comparison with other studies that included this question. Participants were also asked, "When you eat red meat such as beef, pork, or lamb, how well done is it cooked?" with the following possible responses on the questionnaire, "well-done, medium well done, medium rare, rare, and don't eat red meat."

The 1992/1993 FFQ was validated among 441 Nutrition Cohort members who completed four 24-hour dietary recall interviews and a repeat FFQ.[60] For red meat, the correlation coefficient between the FFQ and dietary recall interview was 0.55 among men and 0.78 in women; between the initial FFQ and the repeat FFQ, the correlation coefficient was 0.81 in men and 0.78 in women.

The 1982 questionnaire asked participants to report the average number of days per week they ate each of the 11 meat items. Intake frequencies of red meat, poultry and fish, and processed meat were computed by summing the number of days per week across individual meat items that contributed to each meat group, and categorizing into quintiles. Foods categorized as red meat were beef, pork, ham, liver, smoked meats, frankfurters/sausage, fried bacon, and fried hamburger; poultry and fish included chicken, fish, and fried chicken/fish; and processed meats included ham, smoked meats, frankfurters/sausage, and fried bacon. Turkey was not included on the 1982 questionnaire but was included on the 1992/1993 questionnaire.

We examined long-term meat consumption by considering consumption reported in 1982 and in 1992/1993. Consumption at each time point was categorized into tertiles (low, moderate, high) and participants were classified as low intake in 1982 and 1992/1993 (referent group), high intake in 1982 and 1992/1993, and all other combinations of intake over time.

Statistical Analysis

Colon and rectal cancer incidence rate ratios (RRs) and 95% CIs by meat intake were estimated using Cox proportional hazards regression modeling. *P* values for linear trend were estimated by modeling meat intake (g/wk) using the median value within quintiles; these results were similar when modeled as continuous variables. This study was observational, not randomized, so *P* values were interpreted as approximate.[61] To obtain *P* values and confidence limits, we treated the disease outcome as though it were a random variable that changed over time. Potential confounders were chosen based on a priori considerations and on the observed association with colon or rectal cancer and meat intake.

For each meat variable, we constructed 3 models stratified by single year of age, controlling for other covariates. Model 1 also included total energy (continuous); model 2 included total energy, education (some high school, high school graduate, some college or trade school, college graduate or postgraduate work, or unknown), body mass index calculated as weight in kilograms divided by the square of height in meters in 1992/1993 ($<$18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9, $\geq$40.0, or unknown), cigarette smoking in 1992/1993 (never, former, current, ever smoker not specified, or unknown), recreational physical activity in 1992/1993 (none, hours per week of walking, or walking plus other activities), multivitamin use in 1982 (none, current user, or unknown), aspirin use in 1982 and in 1992 (nonuser in 1982 and 1992, $\geq$15 days per month in 1982 and 1992, $<$15 days per month in 1982 or 1992, or unknown at either time point), intake of wine (none, any), beer (none, any), and liquor (none, any), and hormone therapy use in 1992/1993 among women (nonuser, former user, current user, ever user not specified, or unknown). Model 3 included all covariates in model 2 plus intake of fruits in 1992/1993 (quintiles), vegetables in 1982 (quintiles), and high-fiber grain foods in 1982 (quintiles). Models of men and women combined also included a term for sex. Family history of colorectal cancer reported in 1982 was examined and excluded as a potential confounder; no information on fam-

ily history of colorectal cancer was available in 1992/1993. Results of models including age and energy were similar to those from models including only age or age plus energy in quintiles. In a subanalysis of meat consumption reported in 1992/1993, we examined quintiles of energy-adjusted intake of red meat, poultry and fish, and processed meat based on the residual method.[62] We also examined how the association with each type of meat was affected when controlling for other types of meat; no substantial difference was observed in these analyses (results not shown).

We tested the proportional hazard assumption for each meat intake variable in relation to colon or rectal cancer using the likelihood ratio test, comparing models with and without product terms for meat consumption (quintiles) and follow-up time (years). We evaluated effect modification of the RR for colon and rectal cancer in relation to meat consumption by other covariates using the likelihood ratio test comparing models with and without interaction terms. The Wald statistic was used to test for homogeneity of the RR for proximal and distal colon cancers.[63] All *P* values were 2-sided and considered significant at $P<.05$. All analyses were conducted using SAS version 9.0 (SAS Institute Inc, Cary, NC).

RESULTS

Participant Characteristics by Meat Consumption

Men and women reported a wide range in consumption of red and processed meat in 1992/1993. A 10-fold difference was observed between the lowest and highest quintiles of red meat in men and a 17-fold difference in women (TABLE 1). Men reported greater consumption of red and processed meat than did women; median intake was 427 g/wk and 274 g/wk for red meat among men and women, respectively, and 95 g/wk and 43 g/wk for processed meat, respectively. There was little variation in the consumption of poultry and fish by quintiles of red meat intake. Men also reported substantially higher intake of red and processed meats in 1982 than did women (data not shown). Approximately half of the men and women in the top tertile for consumption of red or processed meat in 1982 were also in the highest tertile in 1992/1993 (data not shown). The absolute levels of meat consumption in 1982 could not be

Table 1. Selected Characteristics of Study Participants by Red Meat Consumption in the Year Before Study Enrollment*

	Red Meat Consumption Reported in 1992 by Quintile, g/wk									
	Men (n = 69 664)					Women (n = 78 946)				
	≤180	181-320	321-480	481-800	>800	≤90	91-240	241-320	321-560	>560
No. of participants	11 615	13 161	14 697	18 811	11 380	11 590	22 804	11 256	21 150	12 146
Meat consumption reported in 1992, g/wk										
Median total meat intake	494	563	704	942	1394	409	466	575	735	1077
Median red meat intake	100	253	398	612	999	43	168	278	416	712
Median processed meat intake	10	54	99	161	283	0	25	51	78	145
Median poultry and fish intake	396	307	299	311	331	369	293	293	305	319
Median ratio of red meat to poultry and fish	0.23	0.82	1.32	1.97	3.17	0.10	0.55	0.95	1.39	2.35
Prefers red meat well done, %	22	21	21	22	24	24	29	29	30	33
Race, nonwhite, %	3	2	2	2	2	3	3	2	2	2
Education, none beyond high school, %	17	21	24	30	38	26	33	35	38	44
No recreational physical activity in 1992, %	7	9	11	14	18	6	8	9	10	13
Median BMI in 1992	25	26	26	26	27	23	24	25	25	27
Current cigarette smoking in 1992, %	4	6	8	11	14	5	7	9	9	11
Any beer consumption in 1992, %	40	47	49	51	51	12	15	17	18	19
Any wine consumption in 1992, %	45	43	41	38	32	43	44	44	41	35
Any liquor consumption in 1992, %	34	41	42	43	41	20	27	30	31	29
Multivitamin use in 1982, %	36	33	31	29	26	46	42	41	39	36
Aspirin use of ≥15 d/mo in 1982, %	9	8	8	8	8	8	8	9	10	10
Current use of hormone therapy in 1992, %						35	34	33	32	29
Median daily energy intake in 1992, calories	1322	1450	1632	1903	2387	1061	1134	1268	1422	1749
<1 Serving/d of fruits in 1992, %	18	24	24	25	27	18	22	22	22	22
Low or no vegetable intake in 1982, %	14	17	18	19	21	17	21	22	23	24
No intake of high-fiber grain foods in 1982, %	17	19	20	22	27	15	16	17	18	20

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters.
*Proportions standardized to the age distribution of the Cancer Prevention Study II Nutrition Cohort, 1992/1993. Due to the large size of the study population, all comparisons across categories of red meat consumption were statistically significant (all $P<.001$).

compared with consumption in 1992/1993 due to differences in the questionnaires.

Men and women who reported higher intake of red meat in 1992/1993 (Table 1) were more likely to report lower educational attainment, no recreational physical activity, higher body mass index, current cigarette smoking, beer and liquor drinking, higher total daily energy intake, low fruit intake in 1992/1993, and little or no intake of vegetables or high-fiber grain foods in 1982 compared with those with lower red meat intake. Men and women who reported lower red meat intake tended to report multivitamin use in 1982, wine drinking, and (in women) use of hormone therapy in 1992/1993.

Meat Consumption and Colon Cancer Incidence

TABLE 2 shows the relationship between colon cancer incidence and meat consumption as reported in 1992/1993. Higher intake of red and processed meat was associated with higher colon cancer risk in men and women in models that adjusted only for age and energy intake (model 1). However, the positive associations were attenuated in analyses (model 2) that further adjusted for nondietary factors, including education, body mass index, cigarette smoking, recreational physical activity, use of multivitamins or aspirin, and (in women) use of hormone therapy. Further adjustment for di-

Table 2. Meat Consumption Reported by Men and Women in 1992/1993 and Colon Cancer Cases by Quintile for All 3 Models*

	Meat Consumption Reported in 1992/1993 by Quintile					*P* Value for Trend
	1	2	3	4	5	
Red Meat						
Men (n = 665)						
No. of colon cancer cases	88	121	141	191	124	
Model 1 RR†	1.00	1.22	1.31	1.46	1.70	<.001
Model 2 RR‡	1.00	1.15	1.19	1.26	1.35	.04
Model 3 RR (95% CI)§	1.00	1.14 (0.86-1.50)	1.16 (0.88-1.53)	1.22 (0.92-1.61)	1.30 (0.93-1.81)	.08
Women (n = 532)						
No. of colon cancer cases	76	154	72	144	86	
Model 1 RR†	1.00	1.02	0.99	1.07	1.14	.09
Model 2 RR‡	1.00	0.99	0.95	0.98	0.99	.40
Model 3 RR (95% CI)§	1.00	0.98 (0.74-1.30)	0.94 (0.68-1.31)	0.98 (0.73-1.32)	0.98 (0.68-1.40)	.45
Men and women (N=1197)						
Model 3 RR (95% CI)§	1.00	1.07 (0.88-1.31)	1.07 (0.86-1.31)	1.11 (0.91-1.36)	1.15 (0.90-1.46)	.04
Processed Meat						
Men (n = 665)						
No. of colon cancer cases	64	125	225	108	143	
Model 1 RR†	1.00	0.81	1.17	1.34	1.39	<.001
Model 2 RR‡	1.00	0.77	1.05	1.15	1.16	.01
Model 3 RR (95% CI)§	1.00	0.75 (0.55-1.02)	1.02 (0.76-1.36)	1.11 (0.80-1.54)	1.11 (0.80-1.54)	.03
Women (n = 532)						
No. of colon cancer cases	89	125	96	104	118	
Model 1 RR†	1.00	1.12	0.98	0.99	1.28	.13
Model 2 RR‡	1.00	1.11	0.95	0.94	1.16	.44
Model 3 RR (95% CI)§	1.00	1.11 (0.84-1.46)	0.95 (0.71-1.27)	0.94 (0.70-1.26)	1.16 (0.85-1.57)	.48
Men and women (N=1197)						
Model 3 RR (95% CI)§	1.00	0.90 (0.74-1.11)	1.01 (0.83-1.23)	1.02 (0.82-1.27)	1.13 (0.91-1.41)	.02
Poultry and Fish						
Men (n = 665)						
No. of colon cancer cases	148	95	189	104	129	
Model 1 RR†	1.00	0.75	0.85	0.77	0.79	.09
Model 2 RR‡	1.00	0.78	0.91	0.85	0.89	.48
Model 3 RR (95% CI)§	1.00	0.78 (0.60-1.02)	0.93 (0.75-1.16)	0.87 (0.67-1.13)	0.92 (0.72-1.19)	.67
Women (n = 532)						
No. of colon cancer cases	135	97	134	79	87	
Model 1 RR†	1.00	0.96	0.80	0.74	0.71	.01
Model 2 RR‡	1.00	0.98	0.84	0.78	0.76	.04
Model 3 RR (95% CI)§	1.00	0.98 (0.76-1.28)	0.84 (0.66-1.07)	0.78 (0.59-1.04)	0.75 (0.56-1.00)	.03
Men and women (N=1197)						
Model 3 RR (95% CI)§	1.00	0.87 (0.73-1.05)	0.89 (0.75-1.05)	0.83 (0.68-1.00)	0.84 (0.70-1.02)	.08

(continued)

etary factors (model 3) had little effect on the RR estimates. No association was observed between colon cancer incidence and consumption frequency of beef, pork, or lamb as a main dish, or with reported preference for red meat doneness (data not shown).

Higher consumption of poultry and fish was inversely associated with colon cancer risk in women but not men (Table 2). Further adjustment for additional covariates other than energy attenuated the association. Among women, the inverse relationship remained statistically significant ($P=.03$ for trend). The positive association between colon cancer risk and ratio of red meat-to-poultry and fish intake was also stronger in women than men. The trend test for the ratio of red meat-to-poultry and fish intake was statistically significant in men, women, and both sexes combined. The inverse, marginally significant, association between high consumption of poultry and fish and colon cancer risk in men and women remained unchanged when adjusting simultaneously for red meat (data not shown).

Proximal and Distal Colon Cancer, and Rectal Cancer

TABLE 3 shows the relationship between meat consumption reported in 1992/1993 and incident colon cancer by subsite and rectal cancer in men and women combined. After covariate adjustment, no consistent association was observed between consumption of red meat, poultry and fish, or processed meat as reported at a single time point and cancer of either subsite of the colon. Men and women in the second to fifth quintiles of red meat intake had higher risk of rectal cancer compared with those in the lowest quintile, particularly those individuals in the highest quintile (RR, 1.71; 95% CI, 1.15-2.52; $P=.007$ for trend). This association was observed primarily with cancers of the rectosigmoid junction (RR, 2.40; 95% CI, 1.30-4.43) with risk increasing significantly with the amount of red meat consumed ($P=.002$ for trend). No significant association was observed between red meat consumption and cancers of the rectum (data not shown). No clear association was observed between rectal cancer risk and other measures of meat consumption reported in 1992/1993.

Energy-Adjusted Meat Intake

Analyses using energy-adjusted meat intake reported in 1992/1993 yielded results similar to those using meat intake (g/wk) with few exceptions. Compared with risk estimates derived from nonenergy-adjusted meat intake, the association between colon cancer and consumption of processed meat (RR, 1.35; 95% CI, 1.04-1.77; highest to lowest quintile, $P=.02$ for trend) became stronger in men, although the association between rectal cancer and red meat intake (RR, 1.31; 95% CI, 0.96-1.79; $P=.03$ for trend) was attenuated in men and women combined. Other risk estimates for red meat, poultry and fish, and processed meat remained unchanged.

Long-term Meat Consumption

TABLE 4 presents multivariate-adjusted RRs for colon cancer by subsite and rectal cancer among persons who were in the highest tertile of meat consumption in both 1982 and 1992/1993 compared with those in the low-

Table 2. Meat Consumption Reported by Men and Women in 1992/1993 and Colon Cancer Cases by Quintile for All 3 Models* (cont)

	Meat Consumption Reported in 1992/1993 by Quintile					*P* Value for Trend
	1	2	3	4	5	
	Ratio of Red Meat to Poultry and Fish					
Men (n = 665)						
No. of colon cancer cases	102	114	179	110	160	
Model 1 RR†	1.00	1.14	1.24	1.46	1.49	.01
Model 2 RR‡	1.00	107	1.11	1.25	1.23	.02
Model 3 RR (95% CI)§	1.00	1.05 (0.80-1.38)	1.09 (0.85-1.40)	1.22 (0.92-1.62)	1.18 (0.90-1.54)	.03
Women (n = 532)						
No. of colon cancer cases	134	112	85	52	149	
Model 1 RR†	1.00	1.13	1.27	1.19	1.48	<.001
Model 2 RR‡	1.00	1.11	1.22	1.12	1.35	<.001
Model 3 RR (95% CI)§	1.00	1.12 (0.87-1.44)	1.23 (0.93-1.62)	1.12 (0.81-1.56)	1.37 (1.06-1.76)	<.001
Men and women (N=1197)						
Model 3 RR (95% CI)§	1.00	1.09 (0.91-1.31)	1.15 (0.96-1.38)	1.21 (0.98-1.49)	1.27 (1.06-1.53)	<.001

Abbreviations: CI, confidence interval; RR, rate ratio.

*Proportions standardized to the age distribution of the Cancer Prevention Study II Nutrition Cohort, 1992/1993 through August 31, 2001. For red meat, the range in men and women for each quintile (g/wk) were as follows: quintile 1 (≤180, ≤90), quintile 2 (181-320, 91-240), quintile 3 (321-480, 241-320), quintile 4 (481-800, 321-560), quintile 5 (>800, >560); for processed meat, quintile 1 (0, 0), quintile 2 (≤60, ≤30), quintile 3 (61-160, 31-60), quintile 4 (161-240, 61-120), quintile 5 (>240, >120); for poultry and fish, quintile 1 (≤160), quintile 2 (161-240), quintile 3 (241-400), quintile 4 (401-560), quintile 5 (>560); for ratio of red meat to poultry and fish, quintile 1 (≤0.5, ≤0.5), quintile 2 (0.6-1.0, 0.6-1.0), quintile 3 (1.1-2.0, 1.1-1.5), quintile 4 (2.1-3.0, 1.6-2.0), quintile 5 (>3.0, >2.0). The quintiles for poultry and fish consumption were nearly identical for men and women; therefore, only 1 range is given. In contrast, men tended to eat more red meats than women; therefore, both boundaries are given for red meat, processed meat, and ratio of red meat to poultry and fish.

†Model 1 includes age, total energy, and sex (both).

‡Model 2 includes age, total energy, education, body mass index, cigarette smoking, recreational physical activity, multivitamin use, aspirin use, beer, wine, liquor, use of hormone therapy (women), and sex (both).

§Model 3 includes age, total energy, education, body mass index, cigarette smoking, recreational physical activity, multivitamin use, aspirin use, beer, wine, liquor, use of hormone therapy (women), sex (both), fruits, vegetables, and high-fiber grain foods.

est tertile at both time points. Prolonged high consumption of red meat was associated with a statistically nonsignificant increased risk of distal colon cancer (RR, 1.29; 95% CI, 0.88-1.89). The most consistent associations were observed between distal colon cancer and prolonged high intake of processed meat (RR, 1.50; 95% CI, 1.04-2.17), and ratio of red meat to poultry and fish (RR, 1.53; 95% CI, 1.08-2.18) compared with persons with prolonged low intake. These associations were not observed with cancer of the proximal colon. The association between distal colon cancer and consumption of processed meat was stronger in analyses based on long-term consump-

Table 3. Meat Consumption of Men and Women Combined Reported in 1992/1993 and Proximal Colon, Distal Colon, and Rectal Cancer Cases by Quintile*

	Meat Consumption Reported in 1992/1993 by Quintile†					*P* Value for Trend
	1	2	3	4	5	
Red Meat						
Proximal colon (n = 667)						
No. of cases	88	169	112	182	116	
Model 3 RR (95% CI)‡	1.00	1.21 (0.93-1.58)	1.08 (0.81-1.44)	1.17 (0.89-1.53)	1.27 (0.91-1.76)	.05
Distal colon (n = 408)						
No. of cases	69	76	79	120	64	
Model 3 RR (95% CI)‡	1.00	0.72 (0.52-1.00)	0.89 (0.64-1.24)	0.87 (0.63-1.21)	0.71 (0.47-1.07)	.92
Rectosigmoid and rectum (n = 470)						
No. of cases	57	118	85	114	96	
Model 3 RR (95% CI)‡	1.00	1.43 (1.03-1.96)	1.26 (0.89-1.78)	1.18 (0.84-1.67)	1.71 (1.15-2.52)	.007
Processed Meat						
Proximal colon (n = 667)						
No. of cases	96	133	174	131	133	
Model 3 RR (95% CI)‡	1.00	0.79 (0.61-1.03)	0.92 (0.71-1.19)	1.03 (0.78-1.35)	0.97 (0.72-1.29)	.17
Distal colon (n = 408)						
No. of cases	44	98	111	58	97	
Model 3 RR (95% CI)‡	1.00	1.19 (0.83-1.70)	1.15 (0.80-1.65)	0.95 (0.63-1.43)	1.39 (0.94-2.05)	.11
Rectosigmoid and rectum (n = 470)						
No. of cases	50	106	134	86	94	
Model 3 RR (95% CI)‡	1.00	1.14 (0.81-1.60)	1.24 (0.88-1.74)	1.31 (0.91-1.88)	1.26 (0.86-1.83)	.18
Poultry and Fish						
Proximal colon (n = 667)						
No. of cases	155	118	174	98	122	
Model 3 RR (95% CI)‡	1.00	0.99 (0.78-1.26)	0.89 (0.71-1.11)	0.82 (0.63-1.07)	0.89 (0.69-1.15)	.23
Distal colon (n = 408)						
No. of cases	102	59	112	62	73	
Model 3 RR (95% CI)‡	1.00	0.72 (0.52-1.00)	0.81 (0.62-1.07)	0.73 (0.53-1.01)	0.73 (0.53-1.01)	.16
Rectosigmoid and rectum (n = 470)						
No. of cases	103	86	127	69	85	
Model 3 RR (95% CI)‡	1.00	1.07 (0.80-1.43)	0.97 (0.74-1.26)	0.87 (0.64-1.19)	0.93 (0.68-1.26)	.69
Ratio of Red Meat to Poultry and Fish						
Proximal colon (n = 667)						
No. of cases	133	134	143	84	173	
Model 3 RR (95% CI)‡	1.00	1.18 (0.92-1.50)	1.18 (0.92-1.51)	1.19 (0.89-1.58)	1.33 (1.04-1.70)	<.001
Distal colon (n = 408)						
No. of cases	85	70	89	62	102	
Model 3 RR (95% CI)‡	1.00	0.92 (0.67-1.26)	1.01 (0.74-1.38)	1.22 (0.87-1.72)	1.13 (0.83-1.55)	.002
Rectosigmoid and rectum (n = 470)						
No. of cases	97	84	108	57	124	
Model 3 RR (95% CI)‡	1.00	1.00 (0.74-1.34)	1.09 (0.82-1.46)	1.00 (0.71-1.41)	1.21 (0.91-1.62)	.43

Abbreviations: CI, confidence interval; RR, rate ratio.
*Proportions standardized to the age distribution of the Cancer Prevention Study II Nutrition Cohort, 1992/1993 through August 31, 2001.
†For red meat, the range in men and women for each quintile (g/wk) were as follows: quintile 1 (≤180, ≤90), quintile 2 (181-320, 91-240), quintile 3 (321-480, 241-320), quintile 4 (481-800, 321-560), quintile 5 (>800, >560); for processed meat, quintile 1 (0, 0), quintile 2 (≤60, ≤30), quintile 3 (61-160, 31-60), quintile 4 (161-240, 61-120), quintile 5 (>240, >120); for poultry and fish, quintile 1 (≤160), quintile 2 (161-240), quintile 3 (241-400), quintile 4 (401-560), quintile 5 (>560); for ratio of red meat-to-poultry and fish, quintile 1 (≤0.5, ≤0.5), quintile 2 (0.6-1.0, 0.6-1.0), quintile 3 (1.1-2.0, 1.1-1.5), quintile 4 (2.1-3.0, 1.6-2.0), quintile 5 (>3.0, >2.0). The quintiles for poultry and fish consumption were nearly identical for men and women; therefore, only 1 range is given. In contrast, men tended to eat more red meats than women; therefore, both boundaries are given for red meat, processed meat, and ratio of red meat to poultry and fish.
‡Model 3 includes age, sex, total energy, education, body mass index, cigarette smoking, recreational physical activity, use of hormone therapy (women), multivitamin use, aspirin use, beer, wine, liquor, fruits, vegetables, and high-fiber grain foods.

tion than on that reported only in 1982 (data not shown). Long-term high intake of poultry and fish was marginally associated with lower risk of proximal (RR, 0.77; 95% CI, 0.59-1.02) and distal (RR, 0.70; 95% CI, 0.50-0.99) colon cancer.

Red meat consumption was marginally associated with higher risk of rectal cancer (RR, 1.43; 95% CI, 1.00-2.05); this association was somewhat stronger for cancers of the rectosigmoid junction (RR, 1.75; 95% CI, 1.04-2.96) than for cancer of the rectum (RR, 1.31; 95% CI, 0.79-2.15). The relationship between long-term consumption of red meat, poultry and fish, and risk of colon or rectal cancer remained unchanged when all were included in the same model (data not shown).

Effect Modification

No statistically significant interaction was observed between meat consumption and other known risk factors for colon or rectal cancer on a multiplicative scale.

COMMENT

The association between processed meat consumption and colon cancer risk was independent of other covariates only when intake was measured at 2 time points during a 10-year interval. Moreover, the association was observed consistently only for cancers of the distal colon. Prolonged high consumption of red meat was associated with higher risk of rectal cancer, particularly cancers of the rectosigmoid junction. Prolonged high consumption of poultry and fish was marginally associated with lower risk of proximal and distal colon cancer but not rectal cancer.

A strength of our study was the ability to control for several factors known to influence colon cancer risk. Inadequate control for potential confounding may partly explain the inconsistently observed positive associations between red meat and colon cancer risk in other studies, since some positive articles included in the quantitative reviews[50,51] have adjusted for only age and energy. In our analyses, the association between colon cancer risk and high intake of red (RR, 1.41; 95% CI, 1.12-1.78) and processed meat (RR, 1.33; 95% CI, 1.08-1.64) measured at a single time point is consistent with meta-analysis results,[50] adjusting for age and energy intake. However, the association was substantially attenuated with further adjustment for educational attainment, cigarette smoking, physical activity, and other lifestyle factors associated with red meat intake.

To our knowledge, no study has addressed the relationship between long-

Table 4. Meat Consumption and Meat Intake of Men and Women Reported in 1982 and 1992/1993, and Cases of Proximal Colon, Distal Colon, and Rectal Cancer*

	Meat Consumption Reported in 1982 and 1992/1993		
	Low Intake in 1982 and 1992/1993	All Other Categories	High Intake in 1982 and 1992/1993
Red Meat			
Proximal colon (n = 667)			
No. of cases	120	428	119
Model 3 RR (95% CI)†	1.00	1.00 (0.81-1.24)	1.02 (0.77-1.36)
Distal colon (n = 408)			
No. of cases	57	275	76
Model 3 RR (95% CI)†	1.00	1.29 (0.96-1.74)	1.29 (0.88-1.89)
Rectosigmoid and rectum (n = 470)			
No. of cases	65	316	89
Model 3 RR (95% CI)†	1.00	1.35 (1.02-1.78)	1.43 (1.00-2.05)
Processed Meat			
Proximal colon (n = 667)			
No. of cases	117	428	122
Model 3 RR (95% CI)†	1.00	1.05 (0.85-1.30)	1.14 (0.87-1.50)
Distal colon (n = 408)			
No. of cases	56	273	79
Model 3 RR (95% CI)†	1.00	1.38 (1.03-1.86)	1.50 (1.04-2.17)
Rectosigmoid and rectum (n = 470)			
No. of cases	80	302	88
Model 3 RR (95% CI)†	1.00	1.07 (0.83-1.38)	1.20 (0.87-1.68)
Poultry and Fish			
Proximal colon (n = 667)			
No. of cases	143	430	94
Model 3 RR (95% CI)†	1.00	0.87 (0.71-1.05)	0.77 (0.59-1.02)
Distal colon (n = 408)			
No. of cases	94	255	59
Model 3 RR (95% CI)†	1.00	0.75 (0.59-0.96)	0.70 (0.50-0.99)
Rectosigmoid and rectum (n = 470)			
No. of cases	102	300	68
Model 3 RR (95% CI)†	1.00	0.85 (0.67-1.07)	0.81 (0.58-1.11)
Ratio of Red Meat to Poultry and Fish			
Proximal colon (n = 667)			
No. of cases	110	426	131
Model 3 RR (95% CI)†	1.00	1.10 (0.89-1.37)	1.20 (0.91-1.57)
Distal colon (n = 408)			
No. of cases	58	258	92
Model 3 RR (95% CI)†	1.00	1.23 (0.92-1.65)	1.53 (1.08-2.18)
Rectosigmoid and rectum (n = 470)			
No. of cases	71	299	100
Model 3 RR (95% CI)†	1.00	1.16 (0.89-1.51)	1.33 (0.96-1.85)

Abbreviations: CI, confidence interval; RR, rate ratio.
*Proportions standardized to the age distribution of the Cancer Prevention Study II Nutrition Cohort, 1992/1993 through August 31, 2001.
†Model 3 includes age, sex, total energy, education, body mass index, cigarette smoking, recreational physical activity, use of hormone therapy (women), multivitamin use, aspirin use, beer, wine, liquor, fruits, vegetables, and high-fiber grain foods.

term meat consumption and risk of colon and rectal cancer. The association with distal colon cancer was stronger among persons who reported greater consumption of processed meat at 2 time points during a 10-year interval, as was the risk of cancer of the rectosigmoid junction among those persons who consistently reported high red meat intake. It is possible that true high consumers of red or processed meat were better defined with less measurement error when assessed twice during a 10-year period. It is also plausible that long-term high consumption of red and processed meat may be more strongly associated with colorectal carcinogenesis than short-term or sporadic consumption of meat. Certain components of red meat may affect both early and late stages in the development of neoplasia. Animal studies show that diets high in red meat tend to affect the early aberrant crypt stage of carcinogenesis.[64] To our knowledge, no study has evaluated the importance of continued high exposure to red meat in animal models.

The higher risk associated with prolonged consumption of red meat but not poultry and fish is consistent with other epidemiological studies.[33,34,38,40] The cytotoxic effect of dietary heme has been proposed as a potential mechanism by which red meat increases colorectal cancer risk because of higher heme content in red meat compared with poultry and fish.[65,66] Heme damages the colonic mucosa and stimulates epithelial proliferation in animal studies.[66] Both ingestion of red meat and heme iron supplementation have been shown to increase fecal concentrations of *N*-nitroso compounds[65] and DNA-adducts in human colonocytes.[67,68]

We found that consistently high consumption of processed meat was associated with increased risk of distal colon cancer. Results of prospective studies of colorectal cancer and processed meat have been more consistently positive in Europe[43,45,47] than in the United States.[33,34,39,40,42] Processed meat includes foods preserved by salting, smoking, or the addition of nitrites or nitrates, and high consumption of these foods can increase exposure to nitrosamines and their precursors. The amount of these substances in processed meat likely varied by region and over time but we had no information to assess the impact of these differences in our study results.

Several prospective studies have reported an inverse association between colon cancer risk and prolonged high consumption of poultry and fish.[34,40,41,47,49] However, other studies have found either no association[33,39,42,43,45,48] or increased risk[36,37,46] associated with poultry and fish consumption. The lower risk associated with high consumption of poultry and fish or a low ratio of red meat-to-poultry and fish could be attributed to a displacement of red meat in the diet, but in our study high consumption of poultry and fish remained independently associated with lower risk of colon cancer even when controlling for red meat intake. It is also possible that poultry and fish contain factors that may protect against colon cancer. Poultry contains small amounts of nutrients such as selenium and calcium that have been associated with lower risk of colorectal neoplasia,[69-71] but it is a relatively minor source of these nutrients. Fish is a primary source of omega-3 fatty acids and high intake of fish or fish oil has been inversely associated with colorectal cancer risk in some epidemiological studies.[40,47,72] In experimental studies, omega-3 fatty acids have been shown to inhibit tumor growth and to modulate the expression of proinflammatory genes.[73,74] However, the poultry and fish consumed by CPS II Nutrition Cohort participants consisted mostly of chicken.

Our findings add to the limited prospective data[38,49,75] on meat consumption in relation to rectal cancer. Consumption of red meat, as reported in 1992/1993, was more strongly associated with rectal than colon cancer in our study, as has been reported in some[4,5,20,21] but not all[17,18,23,24,28,29] case-control studies. One recent case-control study found no association between rectal cancer and red meat, poultry and fish, or processed meat consumption but reported increased risk associated with greater doneness of red meat among men.[76] In our study, the positive association and significant dose-response relationship was observed mostly with tumors of the rectosigmoid junction rather than the rectum. Taken together with the higher risk of cancer observed in the distal colon, our results suggest that tumors in the distal portion of the large intestine may be particularly associated with meat consumption. It is possible that concentration of stool in the distal portion of the large intestine may contribute to higher cancer risk by increasing exposure to carcinogens as a result of water resorption during transit through the large intestine.

Our study had several limitations in addition to the measurement error inherent in studies based on FFQs.[77] The 1982 questionnaire did not assess the number of servings of meat per day and could not differentiate persons who ate multiple servings from those who ate meat only once per day; we were also unable to estimate total energy intake from the 1982 diet questionnaire. We had no information on meat cooking methods to estimate exposure to heterocyclic amines or other specific carcinogens produced from pyrolysis of meat[78-82]; our reliance on self-reported data on preference for doneness of meat was likely a crude proxy of the relevant exposures. Although heterocyclic amines are potent mutagens in the Ames assay and are carcinogenic in animal studies, the impact of these compounds on colorectal carcinogenesis in humans is less clear,[81-83] primarily due to the difficulties in measuring exposure and possible interactions between meat and other dietary constituents or genetic susceptibility.[9,84] We had no information on family history of colorectal cancer from the 1992/1993 questionnaire to update this important variable, which could potentially modify the association between meat intake and risk of colorectal cancer. No information was collected on exami-

nation by sigmoidoscopy, colonoscopy, or fecal occult blood test in either the 1982 or 1992/1993 questionnaires. However, in 1997, persons who reported long-term high consumption of red meat were less likely (23%) to have had endoscopy for screening than those persons who reported long-term low intake of red meat (34%). It is difficult to predict the net effect of endoscopy on colorectal cancer incidence. On the one hand, endoscopic removal of precancerous lesions could contribute to lower risk; however, endoscopy could accelerate the diagnosis of some tumors that might not otherwise have been identified during the follow-up period.

The main strengths of this study are its size, the availability of dietary and other exposure information collected prospectively from respondents at 2 time points, and information on major potential confounders. The sample size allowed us to obtain stable estimates of risk and to show differences by colorectal subsite. Our results demonstrate the potential value of examining long-term meat consumption in assessing risk and strengthen the evidence that prolonged high consumption of red and processed meat may increase the risk of cancer in the distal portion of the large intestine.

Author Contributions: As principal investigator, Dr Chao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chao, Thun, McCullough.
Acquisition of data: Thun, Rodriguez, Calle.
Analysis and interpretation of data: Chao, Thun, Connell, McCullough, Jacobs, Flanders, Rodriguez, Sinha, Calle.
Drafting of the manuscript: Chao, Thun.
Critical revision of the manuscript for important intellectual content: Chao, Thun, Connell, McCullough, Jacobs, Flanders, Rodriguez, Sinha, Calle.
Statistical analysis: Chao, Connell, Flanders.
Obtained funding: Thun, Calle.
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Study supervision: Thun, Calle.
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